REMARKS

The Applicants appreciate the Examiner's thorough examination of the subject application and request reconsideration of the subject application based on the following remarks.

Claims 1,.4, 7, and11-13 have been amended. The claims have merely been amended to comply with the formal requirements of §112, second paragraph. No change to the scope or subject matter of the claims has resulted from the instant amendments. No new matter has been introduced by the instant amendment.

The Title of the application has been amended in accordance with the Examiner's suggestion.

An Abstract of the invention is submitted herewith.

A copy of reference KR 1999-79268 and a form 1449, which lists each of the references cited in the International Search Report (Form PCT/ISA/220) which was filed as part of the application package, are enclosed herewith for consideration by the Examiner. Although

Claims 11 and 12 were objected to in the Office Action for being in improper multiple dependant format. Claim 7, as amended, depends only from claim 1. Thus claims 11 and 12 are in proper multiple dependent format.

Claims 1-13 were rejected under 35 U.S.C. §112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

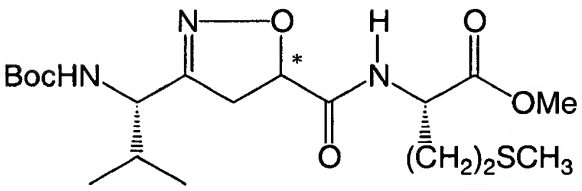
Applicants believe that the amendments to claims 1 and 11-13 obviate the instant rejections and request that the rejections be withdrawn.

Claims 1 and 4 were rejected under 35 U.S.C §102(b) over Ju Young Lee et al. (Journal of the Chemical Society, Perkins Transactions 1: Organic and Bio-Organic Chemistry, January 1998, (2) 359-365).

The rejection is traversed.

The office action cites compound 3 on page 360 of the Lee publication as the basis for the instant rejection.

As the Lee publication is understood, compound 3 corresponds to the formula:



Thus, the Lee compound apparently corresponds to a compound of Formula (I) in which R^2 is hydrogen.

Claims 1 and 4, as amended, provide isoxazoline compounds having a non-hydrogen substituent at R^2. Thus, the Lee publication neither discloses nor suggests the compounds of the claimed invention.

It is believed the application is in condition for immediate allowance, which action is earnestly solicited.

Although it is not believed that any additional fees are needed to consider this submission, the Examiner is hereby authorized to charge our deposit account no. 04-1105 should any fee be deemed necessary.

Respectfully submitted,

Date: April 14, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES TO CLAIMS

Please note that additions to the claims are shown underlined and deletions are shown in brackets.

IN THE SPECIFICATION:

Kindly amend the Title of the Invention on page 1, as follows:

~~CASPASE INHIBITOR~~AN ISOXAZOLINE DERIVATIVE AND A PROCESS FOR THE PREPARATION THEREOF

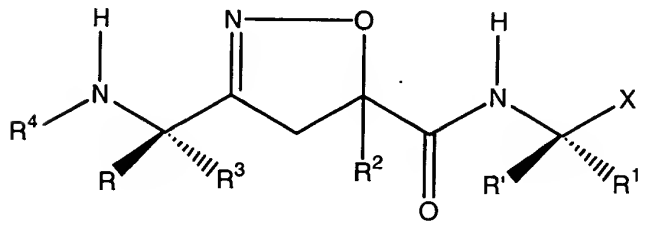
Kindly add an Abstract, as follows:

The present invention provides to an isoxazoline derivative of formula (I), the pharmaceutically acceptable salts, esters and stereochemically isomeric forms thereof, and the use of the derivative in inhibiting the activity of caspases. The present invention also provides a pharmaceutical composition for preventing inflammation and apoptosis which comprise the isoxazoline derivative, pharmaceutically acceptable salts, esters and stereochemically isomeric forms thereof and the process for preparing the same. The derivative according to the present invention can be effectively used in treating diseases due to caspases, such as, for example the disease in which cells are abnormally died, dementia, cerebral stroke, AIDS, diabetes, gastric ulcer, hepatic injury by hepatitis, sepsis, organ transplantation rejection reaction and anti-inflammation.

IN THE CLAIMS:

Kindly amend claims 1, 4, 6, 7, and 11-13, as follows:

1. (Presently Amended) An isoxazoline derivative of the formula (I)



(I)

in which,

R and R' each independently represents hydrogen, simple alkyl chain (-SAC), simple cycloalkyl (-SCAC), aromatic (-Ar), or simple alkyl chain substituted with aromatic (-SAC-Ar);

R^1 represents –SAC, -SCAC, -Ar, or -SAC-Ar, or represents side chain of amino acids, or $-(CH_2)_nCOOZ$ (in which n is 1 or 2, and Z is hydrogen, -SAC, -Ar, or -SCAC);

R^3 represents -SAC, -SCAC, -Ar, or -SAC-Ar, or represents side chain of amino acids;

R^2 represents ~~–H,–~~ SAC, -SCAC, -Ar, or -SAC-Ar, or represents side chain of amino acids, or represents $-(CH_2)_{np}(O)_mR^5$ (in which R^5 = -SAC, -SCAC, -Ar, -SAC-Ar; ~~np~~=0, 1 or 2; and m=0 or 1), or $-(CH_2)_{nq}OC(=O)R^6$ (in which R^6 = -SAC, -SCAC, -Ar, -SAC-Ar; and ~~nq~~=1 or 2);

R^4 represents

a) amino acid residue in which ① the carboxyl group attached to the chiral carbon of amino acid is bound to the amine group to form an amide bond, ② the chiral carbon of amino acid has either R or S configuration, ③ the amino group attached to the chiral carbon of amino acid is protected by formyl, acetyl, propyl, cyclopropylcarbonyl, butyl, methanesulfonyl, ethanesulfonyl, propanesulfonyl, butanesulfonyl, methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, butyloxycarbonyl, methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl,

butylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, dipropylcarbamoyl, dibutylcarbamoyl, or cyclopropylaminocarbonyl, or the amino group may be replaced with a hydrogen atom, and ④ the carboxyl group in the side chain may form an ester group with –SAC or –SCAC,

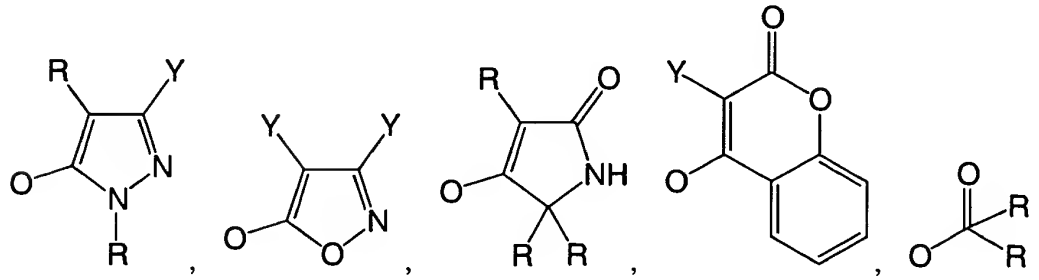
b) -C(=O)R^7 (in which R^7 = -SAC, -SCAC, -Ar, -SAC-Ar), -CO_2R^8 (in which R^8 = hydrogen or R^7), -C(=O)NR^8R^8, -SOR^7, or –C(=O)CH=CH-Ar, or

c) -(C=O)-L-CO_2R^8, in which L represents a divalent (=capable of double substitution) linker selected from a group consisting of C_{1-6} alkyl, C_{3-8} cycloalkyl, furan, thiophene, diazole (1,2 or 1,3), triazole (1,2,3 or 1,3,4), tetrazole, oxazole, isoxazole, thiazole, isothiazole, diazine, (1,2 or 1,3 or 1,4), triazine, -Ph(-R^9)- (in which R^9 = H, F, Cl, Br, I, CHO, OH, OCH_3, CF_3, OCF_3, CN, C(=O)Me), tetrahydrofuran, tetrahydrothiophene, 1,4-dioxane, -CH=C(R^{10})- (in which R^{10}=H, methyl, ethyl), -CH=CHCH(R^{10})-, -CH_2C(=O)CH_2-, and -C(=O)CH_2CH_2-

in cases where R^1 and the adjacent R', and/or R^3 and the adjacent R are connected to each other to form a cyclic compound, R^1-R' or R^3-R together represents -$(CH_2)_n$-, -$(CH_2)_n$-O-$(CH_2)_m$-, or –$(CH_2)_n$-NR^{13}–$(CH_2)_m$- (in which n+m<9, R^{13}=-SAC, -SCAC, -Ar, -SAC-Ar, -C(O)-SAC, -C(=O)-SCAC, -C(=O)-Ar, or –C(=O)-SAC-Ar;

X represents –CN, -CHO, -C(=O)R^{14} (in which R^{14} =-SAC, -SCAC, -Ar, -SAC-Ar, -CHN_2), -C(=O)OR^{15} (in which R^{15} =-SAC, -SCAC, -Ar, or -SAC-Ar), -$CONR^{16}R^{17}$ (in which R^{16} and R^{17} each represents –H, -SAC, -O-SAC, -SCAC, -Ar, or -SAC-Ar), -C(=O)CH_2O(C=O)Ar" (in which A" = 2,6-disubstituted phenyl with F, Cl, Br, I, or CH_3), -C(=O)CH_2OR^{18} (in which R^{18} represents –SAC, -SCAC, -Ar, or –SAC-Ar), or –C(=O)CH_2OC(=O)R^{19} (in which R^{19} = –SAC, -SCAC, -Ar, or –SAC-Ar), or

X represents –$COCH_2$-W, wherein W represents –N_2, -F, -Cl, -Br, -I, -$NR^{20}R^{21}$ or –SR^{22} (in which ~~wherein~~ R^{20}, R^{21} and R^{22} each independently represents –SAC, -SCAC, -Ar, or –SAC-Ar or R^{20} and R^{21} are connected to form a cyclic compound) or W represents



in which Y represents –OH, OR^{23} (in which R^{23} = -SAC, or –SCAC), $-C(=O)R^{24}$ (in which R^{24} = -H, -SAC, or –SCAC), -F, -Cl, -Br, -I, -CN, -NC, $-N_3$, $-CO_2H$, $-CF_3$ $-CO_2R^{25}$ (in which R^{25} = -SAC, or –SCAC), $-C(=O)NHR^{26}$ (in which R^{26} = -SAC, or –SCAC), and $-C(=O)NR^{27}R^{28}$ (in which R^{27}, R^{28} = -SAC, or –SCAC) and can be mono-or poly-substituted at its maximum regardless of the order and the kinds, the pharmaceutically acceptable salts, the esters and the stereochemically isomeric forms thereof.

4. (Presently Amended) The compound of formula (I) according to Claim 1, in which

a) R and R' represent hydrogen,

b) R^1 represents $-CH_2COOH$, $-CH_2COOCH_2$,or $-CH_2COO\ CH_2CH_3$,

c) R^2 represents $-(CH_2)_n(O)_mR^5$ (in which R^5 = -SAC, -SCAC, -Ar, -SAC-Ar; n=0, 1 or 2; and m=0 or 1), -SAC, or -Ar~~, or Hydrogen~~,

d) R^3 represents $-CH(CH_3)_2$, $-CH_2COOH$, $-(CH_2)_2CO_2H$, $-CH_2C(O)NH_2$, or $-(CH_2)_2C(O)NH_2$,

e) R^4 represents $-C(=O)(O)R^{29}$ (in which n=0, 1; R^{29}= -Ar, or –SAC-Ar), $-SO_2R^{30}$ (in which R^{30}= -Ar or –SAC-Ar), or $-C(=O)NHR^{31}$ (in which R^{31} = -Ar, or –SAC-Ar), or

f) X represents $-C(=O)CHN_2$, $-C(=O)CH_2Br$, $-C(=O)CH_2Cl$, $-C(=O)CH_2OPh$, $-C(=O)CH_2OC(=O)Ar''$ (in which Ar''=2,6-dichlorophenyl, 2,6-difluorophenyl or 2,6-dimethylphenyl).

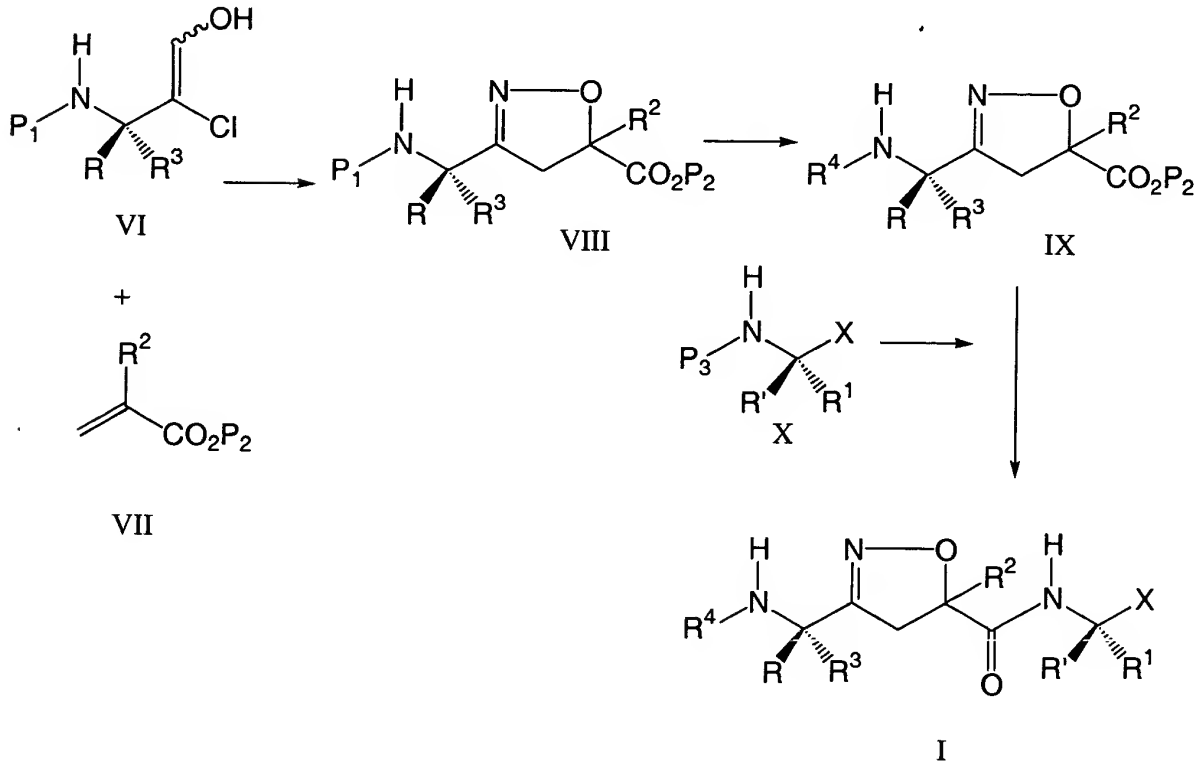
7. (Presently Amended) A pharmaceutical composition for treating disease caused by inflammation or apoptosis which comprises as an active ingredient a therapeutically effective amount of an isoxazoline derivative of the formula (I), the pharmaceutically acceptable salts,

esters or stereochemically isomeric forms thereof as claimed in ~~any one of~~ Claims 1 ~~to 5~~ and pharmaceutically acceptable carrier.

11. (Presently Amended) A method of treating patients suffering from the diseases caused by caspases activation, which comprises a local or systemic administration of a therapeutically effective amount of an isoxazoline derivative of the formula (I), the pharmaceutically acceptable salts, the esters or stereochemically isomeric forms thereof, according to any ~~oen~~one of Claims 1 to 5 or the pharmaceutical composition according to any one of Claims 7 to 10.

12. A process for preparing a pharmaceutical composition for treating disease caused by inflammation or apoptosis which comprises as an active ingredient a therapeutically effective amount of an isoxazoline derivative and pharmaceutically acceptable carrier, the process comprising the step of:
~~the pharmaceutical composition as claimed in any of Claims 7 to 10, characterized in that a pharmaceutically acceptable carrier is~~ intimately ~~mixed~~ mixing a pharmaceutically acceptable carrier with a therapeutically effective amount of a compound of formula (I) as claimed in any of Claims 1 to 5.

13. (Presently Amended) A process for preparing a derivative of the formula (I), the pharmaceutically acceptable salts, esters or stereochemically isomeric forms thereof, characterized in that hydroxamoyl chloride (VI) is reacted with acrylate derivative (VII) to give isoxazoline derivative (VIII), and isoxazoline derivative (VIII) is then deprotected and R^4 is introduced therein to give a compound of formula (IX) which is then reacted with a compound of formula (X) and, if necessary, the isoxazoline derivative (VIII) is directly reacted with the compound (X) to give a compound of formula (I), and if necessary, the compound of formula (I) having the protecting group P_1 is converted into other compound having substitutent R^4.



in which the sustituents are the same as defined in Claim 1.